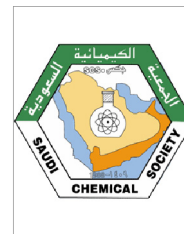




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ORIGINAL ARTICLE

Sulfonated organic heteropolyacid salts as a highly efficient and green solid catalysts for the synthesis of 1,8-dioxo-decahydroacridine derivatives in water



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One-pot synthesis;
Water solvent

Abstract In the present study, we introduce two nonconventional ionic liquids [MIMPS]₃PW₁₂O₄₀ (a) and [TEAPS]₃PW₁₂O₄₀ (b) as green and highly efficient solid acid catalysts for the synthesis of 1,8-dioxo-decahydroacridine derivatives. The one-pot three component reaction of 1,3-cyclohexanediones, aromatic aldehydes and aromatic amines or ammonium acetate in water afforded the corresponding 1,8-dioxo-decahydroacridines in excellent yields. This reaction has been carried out in the presence of 1 mol% of catalysts at room temperature. The reusability of the catalysts was demonstrated by a five-run test. Additionally, the catalysts pose several advantages including mild reaction conditions, cleaner reactions and shorter reaction times.

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1. Introduction

Acridine and acridine-1,8-dione derivatives are polyfunctionalized 1,4-dihydropyridine derivatives. They have a wide range of pharmacological properties such as antimalaria (Spalding

et al., 1954), antitumor (Mikata et al., 1998), anticarcinogenic (Lacassagne et al., 1956), anticancer (Gamega et al., 1999), fungicidal (Wainwright, 2001), cytotoxic (Antonini et al., 1999), anti-multidrug-resistant (Gallo et al., 2003), antimicrobial (Ngadi et al., 1990) and widely prescribed as calcium b-blockers (Bossert and Vater, 1989; Berkan et al., 2002). Also, 1,8-dioxo-decahydroacridines were created to act as laser dyes (Murugan et al., 1998; Islam et al., 2003) and used as photoinitiators (Tu et al., 2004).

Many procedures explained the synthesis of acridine derivatives containing 1,4-dihydropyridines, from dimedone, aldehydes and different nitrogen sources such as urea (Bakibaev et al., 1991), hydroxylamine (Fang et al., 2004), ammonium acetate on basic alumina (Suárez et al., 1999), ammonium

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bicarbonate (Tu et al., 2002), ammonium hydroxide and different appropriate amines or ammonium acetate (Martin et al., 1995), via conventional heating in organic solvents, in the presence of Amberlyst-15 (Das et al., 2006), *p*-dodecylbenzenesulfonic acid (DBSA) (Jin et al., 2004), triethylbenzylammonium chloride (TEBAC) (Wang et al., 2004), Zn(OAc)₂·2H₂O or ammonium chloride or *L*-proline (Balalaie et al., 2009), Proline (Venkatesan et al., 2009), under microwave irradiation (Miao et al., 2002; Wang et al., 2003), and using ionic liquids (Li et al., 2005; Zhang et al., 2006), such as bronsted acidic imidazolium salts containing perfluoroalkyl tails (Shen et al., 2009), 1-methylimidazolium trifluoroacetate ([Hmim]TFA) (Dabiri et al., 2008).

However, some of these reported methods have one or more disadvantages such as moisture sensitive, using the excess of catalysts, prolonged reaction time, low yields, toxic organic solvents, a microwave oven and unpleasant experimental procedure and reagents which are expensive. Performing organic reactions in aqueous media has attracted much attention because of wonderful water properties. It would be significantly safe, cheap, non-toxic and environmentally friendly compared to organic solvents (Li and Chan, 1997). Additionally, the catalyst system can be recycled using the water soluble catalyst and the insoluble products can be separated by simple filtration. So, development of a mild and efficient catalyst system for the synthesis of 1,8-dioxo-decahydroacridines is highly desirable. It should not only be stable in water but also should be completely soluble in it.

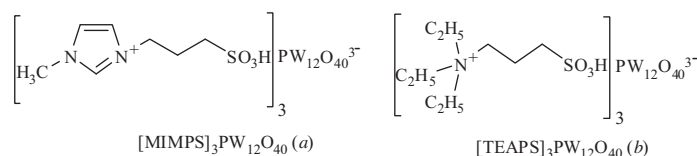
In recent years, ionic liquids have attracted much attention as a new class of green solvents and catalysts (Khalafi-Nezhad and Mokhtari, 2004). These aqueous media is utilized for organic synthesis due to their astonishing properties, such as wide liquid range, favorable solvating capability, low temperature requirement, tunable polarity, high thermal stability, and ease of recyclability (Welton, 1999, 2004; Wasserscheid and Keim, 2000). Ionic liquids also have negligible vapor pressure, which facilitates product separation by distillation. Moreover, they are the cheapest and most environmentally friendly solvents, because water exhibits unique reactivity

and selectivity, which differs from those in conventional organic solvents. The appropriate property of the ionic liquids leads to the development and application of so-called “task-specific” ionic liquids to synthesize the desirable products. Recently, Wang et al. (2009) prepared new heteropolyanion-based ionic liquids containing the acidic functional group as “task-specific” catalysts (*a,b*), (Scheme 1).

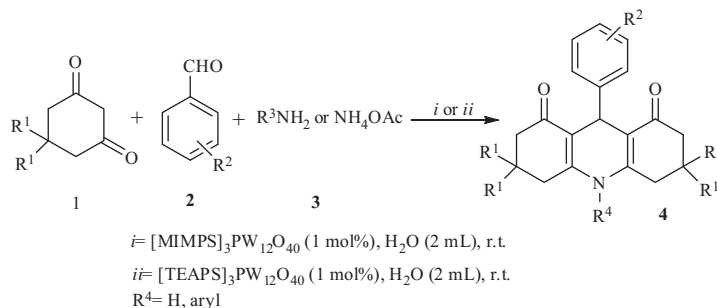
In the present research, we report two green solid catalysts for the synthesis of 1,8-dioxo-decahydroacridine derivatives in aqueous media by the one-pot three component reaction of 1,3-cyclohexanediones, aromatic aldehydes and aromatic amines or ammonium acetate. They pose much higher activity in comparison with the other reported catalysts as well as the additional advantage of reusability. Remarkably, the conventional ionic liquids (ILs) maintain their liquid state at room temperature or to some extent higher (20–30 °C). However, the catalysts used here (*a,b*) exhibit some different and noteworthy properties compared to the other room temperature ionic liquids (RTILs) because of the high value of melting point (above 100 °C). They revealed to be highly efficient green and homogeneous catalysts because of their good solubility in water. Also, the catalyst offers several advantages including mild reaction conditions, shorter reaction times, cleaner reactions, high yield of the products, simply recovered and fairly steadily reused, lower catalytic loading as well as simple experimental and isolation procedures which make it useful for the synthesis of 1,8-dioxo-decahydroacridines.

2. Results and discussion

First, we studied three-component condensation of dimedone (2 mmol), 4-chlorobenzaldehyde (1 mmol) and *p*-toluidine (1 mmol) to optimize the reaction conditions with respect to temperature, time, solvent, molar ratio of catalyst to the substrate and reusability of catalyst. It was found that 1 mol% of catalyst was sufficient to obtain the desired 1,8-dioxo-decahydroacridines in 96% yield within 21 min at room temperature in water (Scheme 2).



Scheme 1 Ionic liquids' (*a,b*) Structure applied in this study.



Scheme 2 Synthesis of 1,8-dioxo-decahydroacridines under condition *i* or *ii*.

After finding the optimized reaction conditions, the investigation was preceded by performing the reaction between a series of aromatic aldehydes and primary amines or ammonium acetate with 1,3-cyclohexanediones. To show the general applicability of this method, various aldehydes and amines were efficiently reacted with two equivalents of 1,3-cyclohexanediones in the same conditions. These results encouraged us to investigate the scope and the generality of this new protocol for various aldehydes and amines under optimized conditions. As shown in Table 1, a series of aromatic aldehydes and amines underwent electrophilic substitution reaction with 1,3-cyclohexanediones to afford a wide range of substituted 1,8-dioxo-decahydroacridines in good to excellent yields. The nature and electronic properties of the substituents on the aromatic ring affect the conversion rate, and aromatic aldehydes having electron-withdrawing groups on the aromatic ring (Table 1, entries 2, 9, 18, 22, 26) react faster than electron-donating groups (Table 1, entries 7, 14, 24, 32, 36). Also, both aromatic amines and ammonium acetate similarly underwent well to the conversion. Notably, the obtained

results depict that the catalyst (a) has more activity than catalyst (b) which is in accordance with that of the PS bearing catalyst.

The effect of solvent on the yield of 1,8-dioxo-decahydroacridines is given in Table 2. The reaction between dimedone, aniline and benzaldehyde was chosen as a model reaction for investigating the effect of solvent. From Table 2 we can know that water is obviously the best choice for these reactions. Another reason we chose water as the solvent of this reaction is that water is a green solvent.

In order to show the merit of ILs in comparison with the other catalysts used for the similar reaction, some of the results are tabulated in Table 3. According to Table 3, the required ratio for the most catalysts used for this purpose is >1 mol% and also the required reaction times are much longer (5–6 h).

So, when isophthalaldehyde (5) was used with 4 molar equivalents of 1,3-cyclohexanediones and 2 molar equivalents of aromatic amines, bisacridine-1,8-diones (6) was obtained in excellent yield (Kaya et al., 2011). The reactions were carried

Table 1 Synthesis of 1,8-dioxo-decahydroacridines under condition *i* or *ii*.^a

Entry	R ¹	R ²	Amine	[MIMPS] ₃ PW ₁₂ O ₄₀		[TEAPS] ₃ PW ₁₂ O ₄₀		M.p. (°C) (Refs.)
				Time (min)	Yield (%) ^b	Time (min)	Yield (%) ^b	
1	H	H	NH ₄ OAc	36	91	57	88	279–280 (Kidwai and Bhatnagar, 2010)
2	H	3-NO ₂	NH ₄ OAc	29	97	47	96	282–284 (Kidwai and Bhatnagar, 2010)
3	H	4-Cl	NH ₄ OAc	31	95	49	94	297–298 (Kidwai and Bhatnagar, 2010)
4	H	2-OH	NH ₄ OAc	34	91	54	91	305–306 (Kidwai and Bhatnagar, 2010)
5	H	4-OH	NH ₄ OAc	33	92	53	91	303–305 (Kidwai and Bhatnagar, 2010)
6	H	2-OMe	NH ₄ OAc	33	91	52	91	300–302 (Kidwai and Bhatnagar, 2010)
7	H	4-OMe	NH ₄ OAc	31	93	50	93	303–305 (Kidwai and Bhatnagar, 2010)
8	Me	H	NH ₄ OAc	33	92	53	89	290–291 (Zhang et al., 2006)
9	Me	3-NO ₂	NH ₄ OAc	23	97	40	96	307–308 (Zhang et al., 2006)
10	Me	4-Cl	NH ₄ OAc	29	95	44	93	298–300 (Kidwai and Bhatnagar, 2010)
11	Me	2-OH	NH ₄ OAc	31	92	50	91	310–311 (Kidwai and Bhatnagar, 2010)
12	Me	4-OH	NH ₄ OAc	29	93	47	91	303–305 (Kidwai and Bhatnagar, 2010)
13	Me	2-OMe	NH ₄ OAc	29	93	47	90	293–295 (Kidwai and Bhatnagar, 2010)
14	Me	4-OMe	NH ₄ OAc	27	92	46	91	276–278 (Kidwai and Bhatnagar, 2010)
15	Me	4-Me	NH ₄ OAc	27	93	44	92	278–280 (Zhang et al., 2006)
16	Me	2,3-(OMe) ₂	NH ₄ OAc	26	93	45	91	325–327 (Zhang et al., 2006)
17	H	H	Aniline	28	92	45	91	274–276 (Venkatesan et al., 2009)
18	H	3-NO ₂	Aniline	21	97	36	97	278–279 (Bhatnagar and Kidwai, 2010)
19	H	4-Cl	Aniline	24	96	39	96	292–293 (Bhatnagar and Kidwai, 2010)
20	H	2-OMe	Aniline	26	94	42	93	270–272 (Chandrasekhar et al., 2008)
21	Me	H	Aniline	25	94	41	92	253–255 (Das et al., 2006)
22	Me	3-NO ₂	Aniline	18	98	23	97	296–297 (Bhatnagar and Kidwai, 2010)
23	Me	4-Cl	Aniline	22	96	35	95	244–246 (Bhatnagar and Kidwai, 2010)
24	Me	2-OMe	Aniline	23	95	35	94	219–221 (Das et al., 2006)
25	Me	H	<i>p</i> -Toluidineiline	26	93	39	92	262–264 (Jin et al., 2004)
26	Me	3-NO ₂	<i>p</i> -Toluidineiline	19	97	31	96	284–286 (Jin et al., 2004)
27	Me	3-Cl	<i>p</i> -Toluidineiline	23	95	35	95	315–316 (Jin et al., 2004)
28	Me	4-Cl	<i>p</i> -Toluidineiline	21	96	33	95	271–273 (Jin et al., 2004)
29	Me	2,4-(Cl) ₂	<i>p</i> -Toluidineiline	22	97	33	94	320–322 (Jin et al., 2004)
30	Me	3,4-(Cl) ₂	<i>p</i> -Toluidineiline	22	96	33	94	251–253 (Shen et al., 2009)
31	Me	4-Me	<i>p</i> -Toluidineiline	23	95	35	95	296–298 (Shen et al., 2009)
32	Me	4-OMe	<i>p</i> -Toluidineiline	25	93	37	92	281–283 (Jin et al., 2004)
33	Me	H	4-Methoxyaniline	26	93	37	93	215–216 (Shen et al., 2009)
34	Me	4-Cl	4-methoxyaniline	20	97	33	95	251–253 (Shen et al., 2009)
35	Me	4-Me	4-Methoxyaniline	23	94	35	94	237–239 (Shen et al., 2009)
36	Me	4-OMe	4-Methoxyaniline	24	93	37	92	212–214 (Shen et al., 2009)

^a Reaction condition: Aromatic aldehyde (1 mmol), 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione (2 mmol), amine (1 mmol) catalyst (1 mol%), solvent (2 mL).

^b Isolated yield.

Table 2 Solvent effect on the reaction between dimedone, aniline and benzaldehyde.^a

Entry	Solvent	[MIMPS] ₃ PW ₁₂ O ₄₀		[TEAPS] ₃ PW ₁₂ O ₄₀	
		Time (min)	Yield (%) ^b	Time (min)	Yield (%) ^b
1	H ₂ O	25	94	41	92
2	C ₂ H ₅ OH	25	94	42	92
3	CH ₃ CN	29	91	45	89
4	CH ₃ COOC ₂ H ₅	33	88	49	84
5	Toluene	37	84	53	82
6	Benzene	41	81	57	78

^a Reaction condition: 5,5-dimethyl-1,3-cyclohexenedione (2 mmol), aniline (1 mmol), benzaldehyde (1 mmol), catalyst (1 mol%), solvent (2 mL).

^b Isolated yield.

Table 3 Comparison reaction between dimedone, 4-chlorobenzaldehyde and *p*-toluidineiline in the presence of different catalysts.^a

Entry	Catalyst	Catalyst (mol %)	Time (min)	Yield (%) ^b	(Refs.)
1	[MIMPS] ₃ PW ₁₂ O ₄₀	1	21	96	This work
2	[TEAPS] ₃ PW ₁₂ O ₄₀	1	33	95	This work
3	PTSA	2	360	18	Dabiri et al. (2008)
4	C ₇ H ₁₅ COOH	2	360	31	Dabiri et al. (2008)
5	DBSA	2	360	41	Dabiri et al. (2008)
6	[HMIM] ⁺ TFA ⁻	0.1 g	300	84	Das et al. (2006)
7	TsOH	10	360	13.2	Jin et al. (2004)
8	Sc(DS) ₃	10	360	78.3	Jin et al. (2004)
9	C ₁₁ H ₁₅ COOH	10	360	26.8	Jin et al. (2004)

^a Reaction condition: Dimedone (2 mmol), aniline (1 mmol), 4-chlorobenzaldehyde (1 mmol).

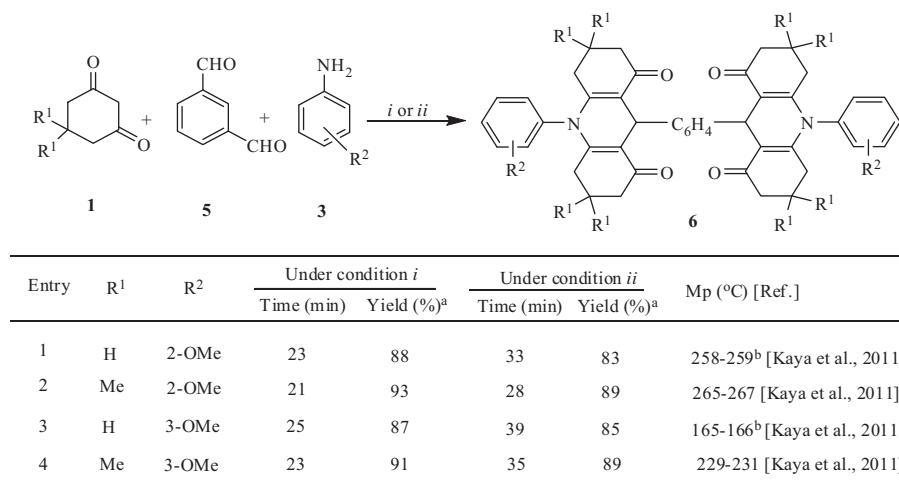
^b Isolated yield.

out fewer than two conditions and the experimental results demonstrate the higher activity of catalyst as compared to catalyst *b*, (Scheme 3).

The high chemoselectivity of this reaction had also been verified by a competitive reaction between dimedone, acetophenone and aniline, as shown in Scheme 4. The result showed that aniline was carried out with dimedone in excellent yield and acetophenone observed with product under identical con-

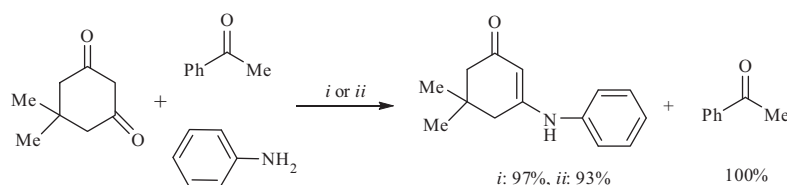
ditions. The high chemoselectivity of this reaction is the result of more reactivity of 1,3-diketone compared with ketone.

The reusability of the catalysts is a significant advantage and makes them useful for commercial applications. The reusability of the catalysts was checked using dimedone, 4-chlorobenzaldehyde and *p*-toluidineiline as a model substrate. At the end of the reaction, CH₂Cl₂ was added to the mixture. The aqueous layer was separated and used without



^a Isolated yield, ^b Decomposition

Scheme 3 Synthesis of bisacridine-1,8-diones under condition *i* or *ii*.



Scheme 4 Chemoselectivity of aniline in the reaction with dimedone in the presence of acetophenone.

Table 4 Reusability studies of the catalyst for synthesis of 9-(4-chlorophenyl)-3,3,6,6-tetramethyl-10-p-tolyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (Table 1, entry 28).^a

Number of experiments	1	2	3	4	6
Isolated yield-under condition <i>i</i> (%) ^b	96	96	95	94	93
Isolated yield-under condition <i>ii</i> (%) ^b	95	94	92	92	91

^a Reaction condition: Dimedone (2 mmol), *p*-toluidineiline (1 mmol), 4-chlorobenzaldehyde (1 mmol), catalyst (1 mol%), solvent (2 mL).

^b Isolated yield.

further purification. In this media, as shown in Table 4, the recovered catalyst can be reused at least five additional times in subsequent reactions without appreciable loss in the catalytic activity.

3. Experimental

All starting materials were obtained from Merck and Fluka, and were used without further purification. Melting points were obtained on a Thermo Scientific apparatus and were not corrected. IR spectra were recorded on a FT-IR Bruker (WQF-510) spectrometer. ¹H and ¹³C NMR spectra were recorded on a Bruker DRX-400 AVANCE spectrometer (400 and 100 MHz, respectively).

3.1. General procedure for the synthesis of 1,8-dioxodecahydroacridine derivatives

A mixture of 1,3-diketone (2.0 mmol), aromatic aldehyde (1.0 mmol), aromatic amine or ammonium acetate (1.0 mmol) and ionic liquids (1 mol%) in water (2 mL) was stirred at room temperature for an appropriate time. The progress of the reaction was monitored by TLC (*n*-hexane/ethyl acetate 4:1). After completion of the reaction, the resulting solid (crude product) was filtered and then recrystallized from ethanol–water to obtain pure product. The physical data (M.p., NMR, IR) of these known compounds were found to be identical with those reported in the literature.

3.2. 3,3,6,6-Tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2H, 5H)-dione (Table 1, entry 8)

M.p. 290–291 °C; IR spectrum (KBr), ν , cm⁻¹: 755 (–CH out of bending of aromatic ring), 1226 (CN stretching), 1486, 1585 (C=C– stretching of aromatic ring), 1635 (C=O– of 1,3-diketone), 2960 (CH stretching of aliphatic), 3054 (–CH stretching of aromatic ring), 3745 (–NH stretching); ¹H NMR spectrum

(400 MHz, DMSO-*d*₆), δ , ppm (*J*, Hz): 0.85 (s, 6H), 1.01 (s, 6H), 1.83–2.49 (m, 8H), 4.83 (s, 1H), 7.02–7.16 (m, 5H), 9.43 (br s, 1H, NH); ¹³C NMR spectrum (100 MHz, DMSO-*d*₆), δ , ppm: 22.1, 26.4, 29.1, 30.2, 30.5, 30.9, 32.3, 32.7, 50.1, 111.4, 114.2, 123.2, 125.1, 126.7, 127.3, 127.7, 146.5, 149.3, 194.1.

3.3. 9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2H, 5H)-dione (Table 1, entry 23)

M.p. 244–246 °C; IR spectrum (KBr), ν , cm⁻¹: 835 (–CH out of bending of aromatic ring), 1247 (CN stretching), 1365, 1587 (C=C– stretching of aromatic ring), 1633 (C=O– of 1,3-diketone), 2955 (CH stretching of aliphatic), 3055 (–CH stretching of aromatic ring), 3745 (–NH stretching); ¹H NMR spectrum (400 MHz, DMSO-*d*₆), δ , ppm (*J*, Hz): 0.83 (s, 6H), 0.95 (s, 6H), 1.80–2.23 (m, 8H), 5.21 (s, 1H), 7.22–7.27 (m, 4H), 7.38–7.58 (m, 5H); ¹³C NMR spectrum (100 MHz, DMSO-*d*₆), δ , ppm: 22.1, 26.7, 29.5, 31.2, 32.3, 32.2, 38.1, 41.8, 50.1, 53.7, 59.6, 114.1, 115.3, 119.3, 128.1, 129.3, 129.4, 129.7, 131.3, 138.8, 144.6, 149.8, 195.5.

3.4. 9,9'-(1,3-Phenylene)-bis-(10-(3-methoxyphenyl)-3,4,6,7-tetrahydroacridine-1,8-(2H, 5H, 9H, 10H)-dione) (Scheme 3, entry 1)

M.p. 258–259 °C; IR spectrum (KBr), ν , cm⁻¹: 835 (–CH out of bending of aromatic ring), 1229 (CN stretching), 1574, 1365 (C=C– stretching of aromatic ring), 1637 (C=O– of 1,3-diketone), 2941 (CH stretching of aliphatic), 3053 (–CH stretching of aromatic ring); ¹H NMR spectrum (400 MHz, DMSO-*d*₆), δ , ppm (*J*, Hz): 1.74–1.91 (m, 4H, 2 * CH₂), 1.925–2.13 (m, 4H, 2 * CH₂), 2.21–2.43 (m, 12H, 6 * CH₂), 2.48–2.55 (m, 2H, CH₂), 2.71–2.75 (m, 2H, CH₂), 3.87 (s, 6H, 2 * OCH₃), 4.83 and 5.34 (2 * d, 2H, *J* = 18.6 Hz, CH), 6.72–6.82 (m, 4H, ArH), 7.05–7.23 (m, 6H, ArH), 7.40–7.53 (m, 2H, ArH).

3.5. 9,9'-(1,3-Phenylene)-bis-(10-(2-methoxyphenyl)-3,4,6,7-tetrahydroacridine-1,8-(2H, 5H, 9H, 10H)-dione) (Scheme 3, entry 3)

M.p. 165–166 °C; IR spectrum (KBr), ν , cm⁻¹: 785 (–CH out of bending of aromatic ring), 1230 (CN stretching), 1574, 1375 (C=C– stretching of aromatic ring), 1634 (C=O– of 1,3-diketone), 2945 (CH stretching of aliphatic), 3065 (–CH stretching of aromatic ring); ¹H NMR spectrum (400 MHz, DMSO-*d*₆), δ , ppm (*J*, Hz): 1.63–1.98 (m, 8H, 4 * CH₂), 2.05–2.33 (m, 12H, 6 * CH₂), 2.51–2.54 (m, 2H, CH₂),

2.64–2.68 (m, 2H, CH₂), 3.93 (s, 6H, 2 * OCH₃), 4.54 and 5.15 (d, 2H, *J* = 15.7 Hz, 2 * CH), 6.52–6.76 (m, 2H, ArH), 6.93–7.15 (m, 5H, ArH), 7.22–7.51 (m, 5H, ArH).

4. Conclusion

In summary, two nonconventional ionic liquids (*a,b*) were used as an efficient catalyst for the synthesis of 1,8-dioxo-decahydroacridines which resulted to better yields. Ionic liquids effectively catalysis the one-pot three-component condensation of 1,3-cyclohexanediones, aromatic aldehydes and aromatic amines or ammonium acetate in water to produce 1,8-dioxo-decahydroacridines in excellent yields. The catalyst offers several advantages including mild reaction conditions, cleaner reactions, shorter reaction times, high yield of the products, lower catalytic loading, high melting point, green solid acid catalyst as well as simple experimental and isolation procedures. Also, the catalysts were able to be reused easily for five-time experiments with a small decrease in the catalytic activity of the recovered catalyst.

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